



IFW

P/1259-765

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Date: July 28, 2004

Fernand LABRIE

Confirmation No.: 9674

Serial No.: 10/749,981

Group Art Unit: 1646

Filed: December 30, 2003

Examiner: --

For: MEDICAL USES OF A SELECTIVE ESTROGEN RECEPTOR MODULATOR
IN COMBINATION WITH SEX STEROID PRECURSORS

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

Submitted herewith is a Form PTO-1449 listing references for consideration by the Examiner. Applicant respectfully requests that the listed references be made of record in the subject application.

In accordance with 37 C.F.R. 1.98(d), copies of any of the listed references which were previously cited by or submitted to the U.S. Patent and Trademark Office in parent application 09/330,799, now U.S. Patent 6,670,346 are not enclosed because such copies are already available in the parent file.

No fee is deemed necessary in connection with the filing of the subject Information Disclosure Statement. However, in the event a fee is required, of if any fee due during the pendency of this application is not paid, the Patent and Trademark Office is authorized to charge the underpayment to Deposit Account No. 15-0700.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450, on July 28, 2004:

Respectfully submitted,

William O. Gray, III

Name of applicant, assignee or
Registered Representative

Signature

July 28, 2004

Date of Signature

William O. Gray, III

Registration No.: 30,944

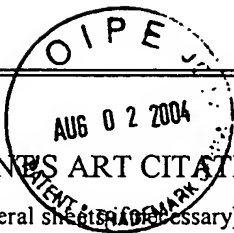
OSTROLENK, FABER, GERB & SOFFEN, LLP

1180 Avenue of the Americas

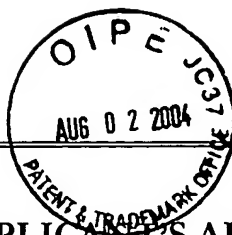
New York, New York 10036-8403

Telephone: (212) 382-0700

WOG:db
Enclosures



APPLICANT'S ART CITATION (Use several sheets if necessary)		Application 10/749,981		OFGS File No. P/1259-765		
		Applicant Fernand Labrie				
		Filing Date December 30, 2003		Group Art Unit 1646		
U.S. PATENT DOCUMENTS (not submitted for applications filed after 6/30/03)						
Examiner Initial	Document Number	Date MM-YYYY	Name	Class	Sub-class	Filing Date If Appropriate
	US-5,840,735	11-1998	Labrie et al.			
	US-5,843,984	12-1998	Clay et al.	514	443	
FOREIGN PATENT DOCUMENTS						
	Document Number	Date MM-YYYY	Country	Class	Sub-class	Translation Yes No
	WO 99/59581	11-1999	WIPO			
	0 781 555	07-1997	European Union			
	WO 93/10741	06-1993	WIPO			
	P 95 01985	07-1996	Hungary			
	P 99 002847	01-1992	Hungary			
	P 98 01230	06-1999	Hungary			
	208150	08-1993	Hungary			
	P 95 00229	05-1996	Hungary			
OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)						
	F. Labrie et al., "DHEA and the Intracrine Formation of Androgens and Estrogens in Peripheral Target Tissues: Its Role During Aging," <i>Steroids</i> , 53:322-328 (1998)					
	F. Labrie et al., "Interactions Between Estrogens, Androgens, Progestins, and Glucocorticoids in ZR-75-1 Human Breast Cancer Cells," <i>Annals New York Academy of Sciences</i> , pp. 130-148, 1990					
	S. Luo et al., "Prevention of Development of Dimethylbenz(a)anthracene (DMBA) - Induced Mammary Tumors in the Rat by the New Nonsteroidal Antiestrogen EM-800 (SCH57050)," <i>Breast Cancer Research and Treatment</i> , 49:1-11 (1998)					
	Schwartz et al., "Dehydroepiandrosterone: an anti-obesity and anti-carcinogenic agent", <i>Nutr. Cancer</i> 1981, 31 (1), 46-53 ISSN: 01635581					
	Couillard, S.; Labrie, C.; Gauthier, S.; Labrie, F., Abstract, <i>Maturitas</i> , (1997), Vol. 27, No. SUPPL., pp. 80, Title: "Inhibitory Effect of a new Non-Steroidal Pure Antiestrogen (EM-800) in Combination with DHEA on Human ZR-75-1 Breast Tumors in Nude Mice"					
Examiner			Date Considered			
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.						



**APPLICANT'S ART
CITATION**

Application No
10/749,981

OFGS File No
P/1259-765

Applicant
Fernand LABRIE

Filing date
December 30, 2003

Group Art Unit
1646

U.S. PATENT DOCUMENTS

Exhibits	Examiner initials	Document number	Date	Name	Class	Sub-class	Filing Date If Appropriate
A		US 3,742,951	July 3, 1973	Zaffaroni			
B		US 3,797,494	Mar. 19, 1974	Zaffaroni			
C		US 4,496,556	Jan. 29, 1985	Orentreich			
D		US 4,542,129	Sep. 17, 1985	Orentreich			
E		US 4,568,343	Feb. 4, 1986	Leeper			
F		US 4,624,665	Nov. 25, 1986	Nuwayser			
G		US 4,666,441	May 19, 1987	Andriola			
H		US 5,064,654	Nov. 12, 1991	Berner			
I		US 5,071,644	Dec. 10, 1991	Viegas			
J		US 5,071,657	Dec. 10, 1991	Oloff			
K		US 5,135,480	Aug. 4, 1992	Bannon			
L		US 5,154,922	Oct. 13, 1992	Govil			
M		US 5,162,037	Nov. 10, 1992	Whitson-Fischman			
N		US 5,354, 861	Oct. 11, 1994	Sim			
O		US 5,362,720	Nov. 8, 1994	Labrie			
P		US 5,391,557	Feb. 21, 1995	Cullinan			
Q		US 5,393,763	Feb. 28, 1995	Black			
R		US 5,393,785	Feb. 28, 1995	Labrie			
S		US 5,395,842	Mar. 7, 1995	Labrie			
T		US 5,489,587	Feb. 6 1996	Fontana			
U		US 5,523,309	Jun. 4, 1996	Bryant			
V		US 5,389,646	Feb. 14, 1995	Labrie			
W		US 5,550,107	Aug. 27, 1996	Labrie			
X		US 5,567,828	Oct. 22, 1996	Dodge			
Y		US 5,686,465	Nov. 11, 1997	Labrie			
Z		US 5,728,688	Mar. 17, 1998	Labrie			

FOREIGN PATENT DOCUMENTS								
Exhibit	Examiner initials	Document number	Date	Name	Class	Sub-class	Translation Yes No	
AA		EP 279982	31.08.88	Nedberge				
BB		EP 635264	25.01.95	Cullinan				
CC		EP 651998A1	10.05.95	Bryant				
DD		EP 652002A1	10.05.95	Williams				
EE		EP 652007A1	10.05.95	Bryant				
FF		EP 657162	14.06.95	Bryant				
GG		EP 665015A2	02.08.95	Black				
HH		EP 674903A1	04.10.95	Draper				
II		EP 693285A2	24.01.96	Black-Cullinan				
JJ		EP 703231	27.03.96	Bryant				
KK		EP 712628	22.05.96	Grese				
LL		EP 724881A1	07.08.96	Leeds				
MM		EP 729955	04.09.96	Cullinan				
NN		EP 747380A1	11.12.96	Dodge				
OO		EP 791591A1	27.08.97	Cullinan				
PP		EP 793961A1	10.09.97	MacLean				
QQ		EP 801066A1	15.10.97	Cullinan				
RR		EP 802183A1	22.10.97	Miller				
SS		EP 802184A1	22.10.97	Miller				
TT		EP 806420A1	12.11.1997	Clay				
UU		GB 1 246 639	15 Sept. 1971	Schering				
VV		GB 2 185 187	15 Jul. 1987	Campbell				
WW		WO 9010462	20.09.90	Labrie				
XX		WO 9300070	07.01.93	Labrie				
YY		WO 9416709	04.08.94	Labrie				
ZZ		WO 9600041	04.01.96	Edwards				
AAA		WO 9605824	29.02.96	Cullinan				
BBB		WO 9605825	29.02.96	Cullinan				
CCC		WO 9605829	29.02.96	Sales				
DDD		WO 9607402	14.03.96	Degregorio				
EEE		WO 9609040	28.03.96	Bryant				
FFF		WO 9616646	06.06.96	Bitonti				
GGG		WO 9626201	29.08.96	Mitchell				
HHH		WO 9725034	17.07.97	Shalmi				
III		WO 9725035	17.07.97	Shalmi				

JJJ		WO 9725036	17.07.97	Korsgaard				
KKK		WO 9725037	17.07.97	Shalmi				
LLL		WO 9725038	17.07.97	Shalmi				
MMM		WO 9732837	12.09.97	Yamamoto				
NNN		WO 8601105	27.02.86	0				

OTHER DOCUMENTS

1.	Adami, S., Baroni, M.C., Brogini, M., Carratelli, L., Caruso, I., Gnessi, L., laurenzi, M., Lombardi, A., Norbiato, G., Ortolani, S., Ricerca, E., Romanini, L., Subrizi, S., Weinberg, J., Yates, A.J. (1993) Treatment of postmenopausal osteoporosis with continuous daily oral alendronate in comparison with either placebo or intranasal salmon calcitonin. <i>Osteoporosis Int. (Suppl.)</i> , 3: S21-S27.
2.	Adams, J., Garcia, M., Rochefort, H. (1981) Estrogenic effects of physiological concentrations of 5-androstene-3 β ,17b-diol and its metabolism in MCF7 human breast cancer cells. <i>Cancer Res.</i> , 41: 4720-4926.
3.	Alison, R.H., Morgan, K.T., Montgomery Jr, C.A. Chapter 26: Ovary. <i>In</i> : Boorman, G.A., Eutis, S.L., Elwell, M.R., Montgomery Jr, C.A. and MacKenzie, W.F., eds, <i>Pathology of the Fischer Rat</i> , pp. 429-442, San Diego: Academic Press, 1990.
4.	Arad, Y., Badimon, J.J., Badimon, L., Hembree, W.C., Ginsberg, H.N. (1989) Dehydroepiandrosterone feeding prevents aortic fatty streak formation and cholesterol accumulation in cholesterol-fed rabbit. <i>Arteriosclerosis</i> , 9: 159-166.
5.	Asselin, J., Kelly, P.A., Caron, M.G., Labrie, F. (1977) Control of hormone receptor levels and growth of 7,12-dimethylbenz(a)anthracene-induced mammary tumors by estrogens, progesterone and prolactin. <i>Endocrinology</i> , 101: 666-671.
6.	Balena, R., Toolan, B.C., Shea, M., Markatos, A., Myers, E.R., Lee, S.C., Opas, E.E., Seedor, J.G., Klein, H., Frankenfield, D., Quartuccio, H., Fioravanti, C., Clair, J., Brown, E., Hayes, W.C., Rodan, G.A. (1993) The effects of 2-year treatment with the aminobisphosphonate alendronate on bone metabolism, bone histomorphometry and bone strength in ovariectomized nonhuman primates. <i>J. Clin. Invest.</i> , 92: 2577-2586.
7.	Baran, D.T., Bergfeld, M.A., Teitelbaum, S.L., Avioli, L.V. (1978) Effect of testosterone therapy on bone formation in an osteoporotic hypogonadal male. <i>Calcif. Tiss. Res.</i> , 26: 103-106.
8.	Bardon, S., Vignon, F., Chalbos, D., Rochefort, H. (1985) RU 486, a progestin and glucocorticoid antagonist, inhibits the growth of breast cancer cells via the progesterone receptor. <i>J. Clin. Endocrinol. Metab.</i> , 60: 692-697.
9.	Barrett-Connor, E., Khaw, K.T., Yen, S.S.C. (1986) A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. <i>New Engl. J. Med.</i> , 315: 1519-1524.
10.	Barrett-Connor, E. (1993) Estrogen and estrogen-progestogen replacement: therapy and cardiovascular diseases. <i>Am. J. Med.</i> , 95 (Suppl. 5A): 40S-43S.
11.	Black, L.J., Sato, M., Rowley, E.R., Magee, D.E., Bekele, A., Williams, D.C., Cullinan, G.J., Bendele, R., Kauffman, R.F., Bensch, W.R., Frolik, C.A., Termine, J.D., Bryant, H.U. (1994) Raloxifene (LY 139481 HCl) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats. <i>J. Clin. Invest.</i> , 93: 63-69.

12.		Boonekamp, P.M., van der Wee-Pals, L.J.A., van Wijk-van Lennep, M.M.L., Wil Thesing, C., Bijovet, O.L.M. (1986) Two modes of action of bisphosphonates on osteoclastic resorption of mineralized matrix. <i>Bone Miner.</i> , 1: 27-39.
13.		Bruning, P.F., Bonfrer, J.M.G., Hart, A.A.M., de Jong-Bakker, M., Linders, D., von Loon, J., Nooyen, W.J. (1988) Tamoxifen, serum lipoproteins and cardiovascular risk. <i>Br. J. Cancer</i> , 58: 497-499.
14.		Bundgaard, H. (1991) In: P. Krogsgaard-Larsen, H.B., ed. Design and application of prodrugs, Switzerland: Harwood Academic Publishers GmFH, Chur, 113-191.
15.		Burger, H., Hailes, J., Nelson, J. (1987) Effect of combined implants of oestradiol and testosterone on libido in postmenopausal women. <i>Br. Med. J.</i> , 294: 936-937.
16.		Carano, A., Teitelbaum, S.L., Konsek, J.D., Schlesinger, P.H., Blair, H.C. (1990) Bisphosphonate directly inhibit the bone resorption activity of isolated avian osteoclasts in vitro. <i>J. Clin. Invest.</i> , 85: 456-461.
17.		Cardy, R.H. (1991) Sexual dimorphism of the normal rat mammary gland. <i>Vet. Pathol.</i> , 28: 139-145.
18.		Chen, C., Bélanger, A., Labrie, F. (1996) Adrenal steroid precursors exert potent androgenic action in the hamster sebaceous glands of flank organs and ears. <i>Endocrinology</i> , 137: 1752-1757.
19.		Cleary, M., Zisk, J. (1983) Effect of dehydroepiandrosterone (DHEA) in adult zucker rats. <i>Fed. Proc.</i> , 42: 536 (abst. 1433).
20.		Colditz, G.A., Hankinson, S.E., Hunter, D.J., Willett, W.C., Manson, J.E., Stampfer, M.J., Hennekens, C., Rosner, B., Speizer, F.E. (1995) The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. <i>N. Engl. J. Med.</i> , 332: 1589-1593.
21.		Coleman, D.L., Schwizer, R.W., Leiter, E.H. (1983) Effect of genetic background on the therapeutic effects of dehydroepiandrosterone (DHEA) in diabetes-obesity mutants and in aged normal mice. <i>Diabetes</i> , 33: 26-33.
22.		Conover, W.J. (1980) Contingency tables. Practical nonparametric statistics, 2nd Edition, pp. 153-170. New York: John Wiley & Sons.
23.		Couillard, S., Labrie, C., Bélanger, A., Candas, B., Pouliot, F., Labrie, F. (1998) Effect of dehydroepiandrosterone and the antiestrogen EM-800 on growth of human ZR-75-1 breast cancer xenografts. <i>J. Natl. Cancer Inst.</i> 90: 772-778.
24.		Dauvois, S., Li, S., Martel, C., Labrie, F. (1989) Inhibitory effect of androgens on DMBA-induced mammary carcinoma in the rat. <i>Breast Cancer Res. Treatm.</i> , 14: 299-306.
25.		Dauvois, S., Spinola, P.G., Labrie, F. (1989) Additive inhibitory effects of bromocriptine (CB-154) and medroxyprogesterone acetate (MPA) on dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in the rat. <i>Eur. J. Cancer Clin. Oncol.</i> , 25: 891-897.
26.		Dauvois, S., Geng, C.S., Lévesque, C., Mérand, Y., Labrie, F. (1991) Additive inhibitory effects of an androgen and the antiestrogen EM-170 on estradiol-stimulated growth of human ZR-75-1 breast tumors in athymic mice. <i>Cancer Res.</i> , 51: 3131-3135.
27.		De Fazio, J., Meldrum, D.R., Winer, J.H., Judd, H.L. (1984) Direct action of androgen on hot flushes in the human male. <i>Maturitas</i> , 6: 3-8.
28.		Diamond, P., Cusan, L., Gomez, J.L., Bélanger, A., Labrie, F. (1996) Metabolic effects of 12-month percutaneous DHEA replacement therapy in postmenopausal women. <i>J. Endocrinol.</i> , 150: S43-S50.
29.		Dipippo, V.A., Lindsay, R., Powers, C.A. (1995) Estradiol and tamoxifen interactions with thyroid hormone in the ovariectomized-thyroidectomized rat. <i>Endocrinology</i> , 136: 1020-1033.
30.		Draper, M.W., Flowers, D.E., Huster, W.J., Neild, J.A., Harper, K., Arnaud, C. (1996) A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. <i>J. Bone Miner. Res.</i> , 11: 835-842.
31.		Gallagher, A., Chambers, T.J., Tobias, J.H. (1993) The estrogen antagonist ICI 182780 reduces cancellous bone volume in female rats. <i>Endocrinology</i> , 133: 2787-2791.

32.		Gauthier, S., Caron, B., Cloutier, J., Dory, Y.L., Favre, A., Larouche, D., Mailhot, J., Ouellet, C., Schwerdtfeger, A., Leblanc, G., Martel, C., Simard, J., Mérand, Y., Bélanger, A., Labrie, C., Labrie, F. (1997) (S)-(+)-4-[7-(2,2-dimethyl-1-oxopropoxy)-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl 2,2-dimethylpropanoate (EM-800): a highly potent, specific, and orally active non steroidal antiestrogen. <i>J. Med. Chem.</i> , 40: 2117-2122.
33.		Gordon, G.B., Bush, D.E., Weisman, H.F. (1988) Reduction of atherosclerosis by administration of dehydroepiandrosterone. <i>J. Clin. Invest.</i> , 82: 712-720.
34.		Gordon, G.B., Helzlsouer, K.J., Comstock, G.W. (1991) Serum levels of dehydroepiandrosterone and its sulfate and the risk of developing bladder cancer. <i>Cancer Res.</i> , 51: 1366-1369.
35.		Harris, S.T., Gertz, B.J., Genant, H.K., Eyre, D.R., Survill, T.T., Ventura, J.N., DeBrock, J., Ricerca, E., Chesnut III, C.H. (1992) The effect of short term treatment with alendronate on vertebral density and biochemical markers of bone remodeling in early postmenopausal women. <i>J. Clin. Endocrinol. Metab.</i> , 76: 1399-1406.
36.		Heaney, R.P., Draper, M.W. (1997) Raloxifen and estrogen: comparative bone-remodeling kinetics. <i>J. Clin. Endocrinol. Metab.</i> , 82: 3425-3429.
37.		Hughes, D.E., MacDonald, B.R., Russell, R.G.G., Gowen, M. (1989) Inhibition of osteoclast-like cell formation by bisphosphonates in long-term cultures of human bone marrow. <i>J. Clin. Invest.</i> , 83: 1930-1935.
38.		Jordan, V.C., Phelps, E., Lindgren, J.U. (1987) Effects of anti-estrogens on bone in castrated and intact female rats. <i>Breast Cancer Res. Treat.</i> , 10: 31-35.
39.		Kaufman, R.F., Bryant, H.U. (1995) Effective therapeutic management of the postmenopausal state will be a cornerstone in strategies for preserving or improving women's health in the 21 st century. Selective estrogen receptor modulators. <i>DN & P</i> 8: 531-539.
40.		Ke, H.Z., Simmons, H.A., Pirie, C.M., Crawford, D.T., Thompson, D.D. (1995) Droloxifene, a new estrogen antagonist/agonist, prevents bone loss in ovariectomized rats. <i>Endocrinology</i> , 136: 2435-2441.
41.		Kent, S. (1982) DHEA: "Miracle" drug? <i>Geriatrics</i> , 37: 157-161.
42.		Kleerekoper, M., Villanueva, A.R., Stanciu, J., Sudhaker Rao, R.D., Parfitt, A.M. (1985) The role of three-dimensional trabecular microstructure in the pathogenesis of vertebral compression fractures. <i>Calcif. Tissue Int.</i> , 37: 594-597.
43.		Koller, C., Buri, P. (1987) Propriétés et intérêt pharmaceutique des gels thermoréversibles à base de poloxamers et polyamines. <i>S.T.P. Pharma</i> , 3: 115-124.
44.		Kramer, C.Y. (1956) Extension of multiple range tests to group means with unequal numbers of replications. <i>Biometrics</i> , 12: 307-310.
45.		Kreitmann, B., Bayard, F. (1979) Androgen interaction with the oestrogen receptor in human tissues. <i>J. Steroid Biochem.</i> , 11: 1589-1595.
46.		Labrie, F., Dupont, A., Bélanger, A. (1985) Complete blockade for the treatment of prostate cancer. <i>In: De Vita, V.T., Hellman, S., Rosenberg, S.A., ed. Importance Advances in Oncology</i> , pp. 193-217. Philadelphia: J.B. Lippincott Co.
47.		Labrie, F. (1991) Intracrinology. <i>Mol. Cell. Endocrinol.</i> , 78: C113-C118.
48.		Labrie, F., Bélanger, A., Simard, J., Luu-The, V., Labrie, C. (1995) DHEA and peripheral androgen and estrogen formation: Intracrinology. <i>Ann. N. Y. Acad. Sci.</i> , 774: 16-28.
49.		Labrie, F., Li, S., Labrie, C., Lévesque, C., Mérand, Y. (1995) Inhibitory effect of a steroidal antiestrogen (EM-170) on estrone-stimulated growth of 7,12 dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the rat. <i>Breast Cancer Res. Treat.</i> , 33: 237-244.

50.	Labrie, F., Simard, J., Luu-The, V., Bélanger, A., Pelletier, G., Morel, Y., Mebarki, F., Sanchez, R., Durocher, F., Turgeon, C., Labrie, Y., Rhéaume, E., Labrie, C., Lachance, Y. (1996) The 3 β -hydroxysteroid dehydrogenase/isomerase gene family: lessons from type II 3 β -HSD congenital deficiency. <i>In</i> : Hansson, V., Levy, F.O. and Taskén, K., eds, Signal Transduction in Testicular Cells. Ernst Schering Research Foundation Workshop, pp. 185-218. Berlin, Heidelberg, New York: Springer-Verlag.
51.	Labrie, F., Luu-The, V., Lin, S.X., Labrie, C., Simard, J., Breton, R., Bélanger, A. (1997) The key role of 17 β -HSDs in sex steroid biology. <i>Steroids</i> , 62: 148-158.
52.	Labrie, F., Bélanger, A., Cusan, L., Candas, B. (1997) Physiological changes in DHEA are not reflected by the serum levels of active androgens and estrogens but of their metabolites: intracrinology. <i>J. Clin. Endocrinol. Metab.</i> , 82: 2403-2409.
53.	Labrie, F., Diamond, P., Cusan, L., Gomez, J.L., Bélanger, A. (1997) Effect of 12-month DHEA replacement therapy on bone, vagina, and endometrium in postmenopausal women. <i>J. Clin. Endocrinol. Metab.</i> , 82: 3498-3505.
54.	Lippman, M.E. (1983) Antiestrogen therapy of breast cancer. <i>Semin. Oncol.</i> , 10: 11-19.
55.	Love, R.R., Newcomb, P.A., Wiebe, D.A., Surawicz, T.S., Jordan, V.C., Carbone, P.P., DeMets, D.L. (1990) Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer. <i>J. Natl. Cancer Inst.</i> , 82: 1327-1332.
56.	Love, R.R., Wiebe, D.A., Newcomb, P.A., Cameron, L., Leventhal, H., Jordan, V.C., Feyzi, J., DeMets, D.L. (1991) Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. <i>Ann. Intern. Med.</i> , 115: 860-864.
57.	Lu, K.H., Chang, R.S., Kledzik, G.S. (1979) Daily patterns of ovarian and pituitary hormone secretion in old female rats just prior to the onset of estrous cycle irregularity and during chronic anovulation. 61st Annual Meeting of the Endocrine Society, p. 106, Abst. No. 134.
58.	Lundeen, S.C., Carver, J.M., McKean, M.L., Winneker, R.C. (1997) Characterization of the ovariectomized rat model for the evaluation of estrogen effects on plasma cholesterol levels. <i>Endocrinology</i> , 138: 1552-1558.
59.	Luo, S., Sourla, A., Labrie, C., Bélanger, A., Labrie, F. (1997) Combined effects of dehydroepiandrosterone and EM-800 on bone mass, serum lipids, and the development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the rat. <i>Endocrinology</i> , 138: 4435-4444.
60.	Martel, C., Sourla, A., Fournier, M., Picard, S., Li, S., Stojanovic, M., Pelletier, G., Labrie, F. (1998) Predominant androgenic component in the stimulatory effect of dehydroepiandrosterone (DHEA) on bone mineral density in the rat. <i>J. Endocrinol.</i> , in press.
61.	Meites, J. (1980) Relation of the neuroendocrine system to the development and growth of experimental mammary tumors. <i>J. Neural. Transmission</i> , 48: 25-42.
62.	Melsen, F., Melsen, B., Mosekilde, L., Bergmann, S. (1978) Histomorphometric analysis of normal bone from the iliac crest. <i>Acta Pathol. Microbiol. Scand.</i> , 86: 70-81.
63.	Morales, A.J., Nolan, A.J., Nelson, J.C., Yen, S.C. (1994) Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. <i>J. Clin. Endocrinol. Metab.</i> , 78: 1360-1367.
64.	Mortensen, L., Charles, P., Bekker, P.J., Digennaro, J., Johnston, C.C. (1998) Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. <i>J. Clin. Endocrinol. Metab.</i> , 83: 396-402.
65.	Need, A.G., Horowitz, M., Bridges, A., Morris, H.A., Nordin, C. (1989) Effects of nandrolone decanoate and antiresorptive therapy on vertebral density in osteoporotic postmenopausal women. <i>Arch. Intern. Med.</i> , 149: 57-60.
66.	Need, A.G., Horowitz, M., Moris, H.A., Walker, C.J., Nordin, B.E.C. (1987) Effects of nadrolone therapy on forearm bone mineral content in osteoporosis. <i>Clin. Orthop.</i> , 225: 273-278.

67.	Odell, W.D., Swerdloff, R.S. (1976) Male hypogonadism. <i>West. J. Med.</i> , 124: 446-475.
68.	Papapoulos, S.E., Landman, J.O., Bijvoet, O.L.M., Lowik, C.W.G.M., Valkema, R., Pauwels, E.K.J., Vermeij, P. (1992) The use of biphosphonates in the treatment of osteoporosis. <i>Bone</i> , 13: S41-S49.
69.	Parfitt, A.M. (1984) The cellular basis of bone remodeling: the quantum concept reexamined in light of recent advances in the cell biology of bone. <i>Calcified Tissue International</i> , 36 Suppl. 1: S37-S45.
70.	Parker, C.R., Simpson, E.R., Bilheimer, D.W., Leveno, K., Carr, B.R., MacDonald, P.C. (1980) Inverse relation between low-density lipoprotein-cholesterol and dehydroisoandrosterone sulfate in human fetal plasma. <i>Science</i> , 208: 512-514.
71.	Podenphant, J., Larsen, N.E., Christiansen, C. (1984) An easy and reliable method for determination of urinary hydroxyproline. <i>Clinica Chimica Acta</i> , 142: 145-148.
72.	Poulin, R., Baker, D., Labrie, F. (1988) Androgens inhibit basal and estrogen-induced cell proliferation in the ZR-75-1 human breast cancer cell line. <i>Breast Cancer Res. Treatm.</i> , 12: 213-225.
73.	Poulin, R., Labrie, F. (1986) Stimulation of cell proliferation and estrogenic response by adrenal C19- Δ^5 -steroids in the ZR-75-1 human breast cancer cell line. <i>Cancer Res.</i> , 46: 4933-4937.
74.	Preston Martin, S., Pike, M.C., Ross, R.K., Jones, P.A., Henderson, B.E. (1990) Increased cell division as a cause of human cancer. <i>Cancer. Res.</i> , 50: 7415-21.
75.	Reginster, J.Y., Deroisy, R., Denis, D., Collette, J., Lecart, M.P., Sarlet, N., Ethgen, D., Franchimont, P. (1989) Prevention of postmenopausal bone loss by tiludronate. <i>Lancet</i> , 2: 1469-1471.
76.	Rossini, M., Gatti, D., Zamberlan, N., Brage, V., Dorizzi, R., Adami, S. (1994) Long-term effects of a treatment course with oral alendronate of postmenopausal osteoporosis. <i>J. Bone Miner. Res.</i> , 9: 1833-1837.
77.	Russell, J.C., Amy, R.M., Graham, S., Wenzel, L.M., Dolphin, P.J. (1993) Effect of castration on hyperlipidemic, insulin resistant JCR: LA-corpulent rats. <i>Atherosclerosis</i> , 100: 113-122.
78.	Russo, I.H., Medado, J., Russo, J. (1989) Endocrine influences on the mammary gland. <i>Monographs on pathology of laboratory animals: integument and mammary glands</i> , pp. 252-266.
79.	Saarto, T., Blomqvist, C., Valimaki, M., Makela, P., Sarna, S., Elomaa, I. (1997) Clodronate improves bone mineral density in post-menopausal breast cancer patients treated with adjuvant antioestrogens. <i>Br. J. Cancer, osteoporosis</i> , 75: 602-605.
80.	Sato, M., Grasser, W., Endo, N., Akins, R., Simmons, H., Thompson, D.D., Golub, E., Rodan, G.A. (1991) Bisphosphonate action. Alendronate localization in rat bone and effects on osteoclast ultrastructure. <i>J. Clin. Invest.</i> , 88: 2095-2105.
81.	Schwartz, A.G. (1979) Inhibition of spontaneous breast cancer formation in female C3H (Avy/a) mice by long-term treatment with dehydroepiandrosterone. <i>Cancer Res.</i> , 39: 1129-1132.
82.	Sherwin, B.B., Gelfand, M.M. (1984) Effects of parenteral administration of estrogen and androgen on plasma hormone levels and hot flushes in the surgical menopause. <i>Am. J. Obstet. Gynecol.</i> , 148: 552-557.
83.	Sherwin, B.B., Gelfand, M.M. (1985) Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. <i>Am. J. Obstet. Gynecol.</i> , 151: 153-160.
84.	Sherwin, B.B., Gelfand, M.M. (1987) The role of androgen in the maintenance of sexual functioning in oophorectomized women. <i>Psychosom Med.</i> , 49: 397-409.
85.	Sherwin, B.B., Gelfand, M.M., Schucher, R., Gabor, J. (1987) Postmenopausal estrogen and androgen replacement and lipoprotein lipid concentrations. <i>Am. J. Obstet. Gynecol.</i> , 156: 414-419.
86.	Sherwin, B.B. (1988) Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. <i>J. Affect. Disord.</i> , 14: 177-187.
87.	Sibonga, J.D., Evans, G.L., Hauck, E.R., Bell, N.H., Turner, R.T. (1996) Ovarian status influences the skeletal effects of tamoxifen in adult rats. <i>Breast Cancer Res. Treatm.</i> , 41: 71-79.

88.		Simard, J., Labrie, F. (1987) Adrenal C19-5-ene steroids induce full estrogenic responses in rat pituitary gonadotrophs. <i>J. Steroid Biochem.</i> 26: 539-546.
89.		Sledge, G.W., McGuire, W.L. (1983) Steroid hormone receptors in human breast cancer. <i>Adv. Cancer Res.</i> , 38: 61-75.
90.		Smith, D.A.S., Walker, M.S. (1976) Changes in plasma steroids and bone density in Klinefelter's syndrome. <i>Calif. Tissue Res.</i> , 22 (Suppl.): 225-228.
91.		Sortino, M.A., Wise, P.M. (1989) Effects of age and long term ovariectomy on prolactin secretion, as assessed by the reverse hemolytic plaque assay. <i>Endocrinology</i> , 124: 90-96.
92.		Storm, T., Thamborg, G., Steiniche, T., Genant, H.K., Sorensen, O.H. (1990) Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. <i>N. Engl. J. Med.</i> , 322: 1265-1271.
93.		Svec, F., Richards, R., Porter, J.R. (1997) The effect of dehydroepiandrosterone (DHEA) on lean Zucker rats. 2nd International Conference on Cortisol & Anti-Cortisols, Las Vegas, Nevada, USA, p. 56 (Abst.).
94.		Tang, F.Y., Bonfiglio, T.A., Tang, L.K. (1984) Effect of estrogen and progesterone on the development of endometrial hyperplasia in the Fischer rat. <i>Biol. Reprod.</i> , 31: 399-413.
95.		Tchernof, A., Després, J.P., Bélanger, A., Dupont, A., Prud'homme, D., Moorjani, S., Lupien, P.J., Labrie, F. (1995) Reduced testosterone and adrenal C19 steroid levels in obese men. <i>Metabolism, osteoporosis</i> , 44: 513-519.
96.		Thoman, M., Weigle, W. (1989) The cellular and subcellular bases of immunosenescence. <i>Adv. Immunol.</i> , 46: 221-260.
97.		Wakeling, A.E. (1993) The future of new pure antiestrogens in clinical breast cancer. <i>Breast Cancer Res. Treat.</i> , 25: 1-9.
98.		Walsh, B.W., Schiff, I., Rosner, B., Greenberg, L., Ravnkar, V., Sacks, F.M. (1991) Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. <i>New Engl. J. Med.</i> , 325: 1196-1204.
99.		Watts, N.B., Harris, S.T., Genant, H.K., Wasnich, R.D., Miller, P.D., Jackson, R.D., Licata, A.A., Ross, P., Woodson, G.C., Yanover, M.J., Mysiw, J., Kohse, L., Rao, M.B., Steiger, P., Richmond, B., Chesnut III, C.H. (1990) Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. <i>N. Engl. J. Med.</i> , 323: 73-79.
100.		Weinstein, R.S., Hutson, M.S. (1987) Decreased trabecular width and increased trabecular spacing contribute to bone loss with aging. <i>Bone</i> , 8: 137-142.
101.		Wilson, T.M., Norris, J.D., Wagner, B.L., Asplin, I., Baer, P., Brown, H.R., Jones, S.A., Henke, B., Sauls, H., Wolfe, S., Morris, D.C., McDonnell, D.P. (1997) Dissection of the molecular mechanism of action of GW5638, a novel estrogen receptor ligand, provides insights into the role of estrogen receptor in bone. <i>Endocrinology</i> , 138: 3901-3911.
102.		Wittliff, J.L. (1984) Steroid-hormone receptors in breast cancer. <i>Cancer</i> , 53: 630-643.
103.		Wolkowitz, O., Reus, V.I., Vinogradov, S., Marco, E., Chan, T., Manfredi, F., Poole, J., Johnson, R., Canick, J., Lichtmacher, J., Keebler, A., Friedland, M., Brizendine, L. (1997) Antiglucocorticoid treatment of depression and schizophrenia: double-blind ketoconazole. 2nd International Conference on Cortisol & Anti-Cortisols, Las Vegas, Nevada, USA, p. 62 (Abst.).
104.		Yen, T.T., Allen, J.A., Pearson, D.V., Acton, J.M. (1977) Prevention of obesity in Avy/a mice by dehydroepiandrosterone. <i>Lipids</i> , 12: 409-413.
105.		Guidelines for preclinical and clinical evaluation of agents used in the prevention or treatment of postmenopausal osteoporosis, Division of Metabolism and Endocrine Drug Products, FDA, May 1994.
106.		abstract of U.S. 5,478,579 7/21/93 Sawruk
107.		abstract of U.S. 5,476,865 7/6/94 Panetta
108.		Minutes of the Endocrinology and Metabolism Drugs Advisory Committee, FDA Thursday, Meeting #68, November 20 th 1997.

109.		Sourla, et al., Endocrinology, 139(2):753-764 (1998)
110.		Hackenberg, et al., J. Steroid Biochem., 46(5):597-603 (1993)
111.		Labrie, et al., J. Steroid Biochem., 69:51-84 (1999)
112.		CA 130:108222, Nawata et al.
113.		CA 129:270586, Clarke et al.
114.		CA 119:108253, Ono
115.		

Examiner	Date considered
----------	-----------------